U.S. Patent Application No.09/913,459
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Applicant : KYOWA HAKKO KOGYO CO., LTD.
Name of the Invention : TABLET AND TABLET PRODUCTION METHOD

I, MOTOHIRO OHTA, of 47-1, Takehara, Nagaizumi-cho, Sunto-gun, Shizuoka, Japan do declare as follows:

Since April, 1978, I have been employed by Kyowa Hakko Kogyo Co., Ltd. I was engaged in the research and development on the pharmaceutical preparation in drug formulation research laboratory and business development Dept. The following experiment was conducted under my direction.

I have a full knowledge of the present invention and cited prior art.

In order to show unobviousness of the present invention, I have conducted the following experiment.

The experiment compared disintegration time and tablet hardness in which mixtures of a saccharide with high wettability against water and a disintegrant are granulated, dried, and tabletted. In Example 1 the mixture is granulated using a solution of binder and a saccharide with high wettability against water; in comparison 1 and 2 the granulating solutions contain only the saccharide (representative of EPO0745382A1 "Process" 1-6 and Examples 1-19, especially Example 4) and binder, respectively.

Materials

<Example 1>

Crosspovidone, as disintegrant, in the amount of 5 volume % of the entire volume was added to D-mannitol powder in an agitating granulator and was mixed for five minutes. After mixing, a solution including lactose in the amount of 5 volume % and hydroxypropylcellulose in the amount of 1 volume % was added for granulation. Then the granulated material was dried for about 15 minutes at 80℃ of intake temperature with a fluid bed dryer and was sized with a No.20 mesh wire.

Magnesium stearate in the amount of 0.5 volume % was mixed with the obtained granulated material to prepare granules for tabletting. The granules were compressed with a rotary type tabletting machine with a circular punch having 7mm diameter, at a tabletting pressure of 700 kg/punch and with a tablet weight of 120mg.

<Comparison 1>

The process according to Example 1 was conducted except that the solution added for granulation after mixing contained lactose in the amount of 5 volume %. Crosspovidone, as disintegrant, in the amount of 5 volume % of the entire volume was added to D-mannitol powder in an agitating granulator and mixed for five minutes. After mixing, a solution including lactose in the amount of 5 volume % was added for granulation. Then the granulated material was dried for about 15 minutes at 80℃ of intake temperature with a fluid bed dryer and was sized with a No.20 mesh wire.

Magnesium stearate in the amount of 0.5 volume % was mixed with the obtained

granulated material to prepare granules for tabletting. The granules were compressed with a rotary type tabletting machine with a circular punch having 7mm diameter, at a tabletting pressure of 700 kg/punch and with a tablet weight of 120mg.

<Comparison 2>
The process according to Example 1 was conducted except that the solution added for granulation after mixing contained hydroxypropylcellulose in the amount of 1 volume %. Crosspovidone, as disintegrant, in the amount of 5 volume % of the entire volume was added to D-mannitol powder in an agitating granulator and mixed for five minutes. After mixing, a solution including hydroxypropylcellulose in the amount of 1 volume % was added for granulation. Then the granulated material was dried for about 15 minutes at 80℃ of intake temperature with a fluid bed dryer and was sized with a No.20 mesh wire.
Magnesium stearate in the amount of 0.5 volume % was mixed with the obtained granulated material to prepare granules for tabletting. The granules were compressed with a rotary type tabletting machine with a circular punch having 7mm diameter, at a tabletting pressure of 700 kg/punch and with a tablet weight of 120mg.

Evaluation
The measuring method was as follows.
The hardness of the tablet was measured by a tablet destructive strength measuring instrument (Toyama Sangyo Co., Ltd. : TH-203CP type).
The intrabuccal disintegration time of the tablet was measured as follows: Each one of five healthy adults took one tablet in the mouth and the time the tablet was dissolved without chewing in the buccal cavity with saliva was measured. The average value of five persons was calculated and considered as disintegration time in the buccal cavity. Results are shown in Table 1 below.

Results

	granulating solution	hardness	disintegration time
Example 1	5% lactose 1% hydroxypropyl cellulose	4.1 kgf	26 sec.
Comparison 1	5% lactose	2.1 kgf	22 sec.
Comparison 2	1% hydroxypropyl cellulose	1.5 kgf	24 sec.

Conclusion
As illustrated, the present invention achieves a tablet with superior hardness which is greatly useful compared to the closest embodiment of the prior art. The result obtained by the present invention would not have been expected by the skilled artisan at the time that invention was made.
I hereby declare that all statements made herein of my own knowledge are

true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Sep 29, 2003 — dated

Motohiro Ohta — Motohiro Ohta